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Chapter Five - Medulloblastoma chapter - past perspectives and future directions

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Abstract

Medulloblastoma, once considered a uniform entity, is now accepted as a complex and heterogeneous group of tumors requiring a nuanced and multidisciplinary approach to diagnosis and treatment. The now four recognized primary subgroups have distinct genetic, epigenetic, and clinical characteristics that influence prognosis and treatment responses necessitating subgroup-specific strategies.

Advances in diagnostics and risk stratification, largely driven by a deeper understanding in tumor biology, has led to an overall improvement in survival (>70%), through risk-adapted treatment strategies. Contemporary clinical approaches incorporate a multimodality treatment strategy, integrating surgery, radiotherapy and intensive chemotherapy, each of which is associated with significant short- and long-term morbidity.

Novel targeted therapeutics continue to be developed, investigated and explored in vitro, in vivo and through clinical trial design, particularly in the high risk and relapsed settings. As the

therapeutic landscape continues to evolve, combining conventional therapies with these approaches holds promise to improve clinical outcomes.

These innovations and developments expanding all disciplines aim to continue to provide precision-based care and enhance survival outcomes across all subgroups whilst mitigating the significant long-term burden of treatment-related sequelae disproportionately experienced by medulloblastoma survivors.

Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children and young people aged 0–19 years, accounting for approximately 20% of all brain tumors and 70% of all embryonal tumors in this age group, with the average annual age-adjusted incidence rate (AAAIR) (with approximately 6 cases per year in 100,000) (Ostrom et al., 2023, Price et al., 2024). Through integrated genomics, our understanding of MB has radically transformed in the past two decades recognizing tumor heterogeneity with biological, clinical, therapeutic and prognostic implications (Lazow et al., 2022). Diagnosis, treatment strategies and prospective clinical trial design for patients with MB are now heavily influenced by the tumor molecular profile in addition to historic risk-factors including age, stage and morphology such as presence of large cell/anaplasia (LCA). Four consensus molecular subgroups are now accepted– WNT (MB_{WNT}), SHH(MB_{SHH}), Group3(MB_{Grp3}) and Group4(MB_{Grp4}) – each with its own genetic profile, presentation and prognosis, the scrutiny of which has led to the understanding of intergroup heterogeneity and recognition of second-generation subgroups (Louis et al., 2021, Sharma et al., 2019).

Well-accepted multimodal regimens that include maximally safe resection, craniospinal irradiation (CSI) and adjunctive chemotherapy have resulted in a significant improvement in long-term survival, with overall survival rate at 70%. Unfortunately, despite these improvements in upfront therapy since the 1990's, patients with recurrent/refractory disease continue to a have dismal prognosis with limited curative salvage options (Sabel et al., 2016).

In addition, survivors of MB suffer substantial tumor and treatment-related burdens. Ongoing efforts to mitigate this morbidity remains a necessary component of any future advances.

Through a synthesis of recent research and clinical insights, this chapter aims to provide a comprehensive understanding of medulloblastoma, underscoring its multifaceted nature and the cruciality of a multidisciplinary approach in guiding treatment decisions in this complex and challenging disease entity (Weil et al., 2017).

Section snippets

Clinical presentation

Medulloblastoma can manifest very differently depending on tumor size, location, and the patient's age. Symptoms can initially be subtle and develop over weeks to months. In children, symptoms often arise from increased intracranial pressure due to obstructive hydrocephalus caused by the tumor's typical location in the posterior fossa. Most commonly, symptoms include morning headaches, nausea, vomiting, and lethargy. Older children and adults may present with ataxia, gait disturbances, and …

Advances in imaging

Magnetic resonance imaging (MRI) remains the cornerstone for the initial diagnosis and surgical planning of medulloblastomas (Fig. 1). The need for meticulous imaging techniques (and reporting) in patients with MB was well demonstrated in the Children's Oncology Group (COG) A9961 clinical trial (Packer et al., 2013). Clinical imaging standards with minimum mandatory sequence acquisition have been published by the Response Assessment in Pediatric Neuro-oncology Committee (RAPNO) to optimize …

Risk stratification

Risk groups are often defined based on current survival rates:

- low risk (>90 % survival), …
- average (standard) risk (75–90 %survival), …
- high risk (50–75 % survival) and …
- very high risk (<50 % survival) disease (Ramaswamy et al., 2016). …

Approximately 30 % of MB patients are diagnosed as high risk. With the advances in genomic signatures, the definition of high-risk features has and will continue to evolve. Expeditious validation of novel molecular markers are essential for effective clinical trial design …

Surgical therapy

Surgery remains the cornerstone of medulloblastoma treatment, with its primary goal being the safe removal of as much tumor as possible. Advanced surgical techniques, including intraoperative use of neuromonitoring (IONM) and neuronavigation, have significantly improved the safety and efficacy of medulloblastoma resections. This section outlines the objectives, techniques, challenges, and technological advances that shape surgical management while addressing potential complications and …

Relapsed medulloblastoma (rMB)

Relapses occur in approximately 30 % of patients with medulloblastoma. Tragically, after multimodal therapy with upfront CSI, it is almost invariably fatal accounting for a significant

proportion of cancer-related childhood deaths (Cooney et al., 2023, O'Halloran et al., 2024).

Substantial advances have gone into understanding rMB biology, prognostic factors and patterns of relapse in the context of molecular subgrouping. Median time to relapse can vary but is notably related to molecular …

Survivorship

Although survival rates have dramatically improved with the use of multi-modal therapies, the long-term negative impact is considerable. Survivors of medulloblastoma are amongst those with the most severe clinical and wide-ranging disabilities. Known risk factors include but are not limited to age at diagnosis and CSI, radiotherapy and cumulative alkylator therapy.

An in-depth review of the late sequelae in medulloblastoma survivors is beyond the scope of this review but we have chosen to expand …

Future directions and challenges

Preclinical models have also played a crucial role in advancing knowledge about medulloblastoma. Animal models, particularly mouse models of MB_{SHH} and MB_{WNT} tumors, and patient-derived xenografts have provided valuable insights into tumorigenesis and the complex signalling pathways driving tumor growth and progression (Roussel and Stripay, 2020, Kawauchi et al., 2012). These models have been instrumental in testing novel therapeutic approaches, offering a bridge between laboratory discoveries …

Conclusion

The story of medulloblastoma is one of remarkable progress and ongoing evolution. From the identification of molecular subgroups to the development of cutting-edge therapies, each advancement has brought us closer to a more comprehensive understanding and effective treatment of this disease.

Despite these strides, significant challenges remain. Translating research into clinical practice is fraught with obstacles, including the heterogeneity of the disease, the high costs of novel therapies, and …

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